HIV-1 drug resistance mutations in children born to mothers on PMTCT in Tanzania

KCMC POST – GRADUATE SEMINAR 22nd – 24thOCTOBER 2014

THEME: INFECTIOUS DISEASES: TRENDS AND THREATS

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Oxford Journal of Antimicrobial Chemotherapy published ON April 11, 2014

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Factors towards HIV- drug resistance

- High replication rate
- High mutation rate resistance
- Latent reservoirs of HIV



Inadequate potency Inadequate durability Drug-drug interactions Poor tolerability Counterfeit

WHO-2012 HIV DRUG RESISTANCE SURVEILLANCE AND MONITORING STRATEGY

Surveillance of	Surveillance of HIVDR in				
transmitted drug	populations initiating				
resistance (TDR) in	ART				
recently infected					
populations Monitoring or	f HIVDR				
early warning indicators					
Surveillance of HIVDR	Surveillance of acquired				
in children <18 months	HIVDR in populations on				
of age	ART for >12 months and				
	<24 months				

Statement of the problem and Justification

»Problem.

- Extensive use of sdNVP for PMTCT increases HIVDR
- Increasing rolling up of ART to the general population means increasing need for HIVDR surveillance.

(HIV/AIDS/STI Surveillance Report no 22 of 2011:Mark Wainberg 2011)

»Justification

- No Information on transmitted HIV-1 subtypes and HIVDR among children ≤18months in Northern Tanzania.
- Implementing new 2012 WHO HIVDR survey among children less than 18 months.

Objectives

Broad objective

To characterize HIV-1 subtypes and determine the prevalence of mutations associated with antiretroviral drug resistance among children ≤18 months in northern Tanzania.

Specific objectives

- 1.To determine the transmitted HIV-1 subtypes among infected children in northern Tanzania
- 2. To determine the prevalence of mutations associated with antiretroviral drug resistance among transmitted HIV-1 subtypes in northern Tanzania

Methodology- cont...

Study- Sites (Northern Tanzania) Zanzibar

Study design- Retrospective cross sectional

1-Kilimanjaro

Study population- HIV+ children ≤18months

3- Manyara

2-Arusha

4- Tanga

Inclusion- ≤18months, PCR+ and ART history

Exclusion-<2 DBS,VL ≤400cps/mL, poor quality sequences

Dependent- HIVDR

Independent-ART regimens, HIV-1 subtypes & VL

Sampling- convenient

Ethical clearance- KCMU-College and BHP

Data analysis- STATA v.11.1, Descriptive analysis (median, IQR, P value ≤0.05)

Figure 1: Sites where HIV-1 infected children \leq 18 months weight ampled

HIV-1 Genes of interest



Approximate recombination pattern without bootstrap confidence© REGA HIV-1 Subtyping ToolSubtype assigned based on sequence > 800 bps clustering with a pure subtype with
bootstrap > 70% without recombination in the bootscan.8



Methodology cont....



Figure 4:Assignment of pure HIV-1subtypes using Rega HIV-1&2 automated subtyping Tool version 2.0 (2012).Showing how HIV-1 subtype C differ from other sequences back ground of A1,G and J

RESULTS

Distribution of HIV-1 Subtypes among Vertically HIV infected children in Northern Tanzania



Figure 5: Percentage distribution of HIV-1 subtypes among HIV-1 infected children <18 months in Northern Tanzania.

RESULTS CONT.....

Table 1:Presence of major HIVDR mutation among children <18months in Northern Tanzania.

ID	HIV-1 Subtypes	MAJOR MUTATIONS	Pre-labor Prophylaxis	Labor Prophylaxis	Infants Prophylaxis	Mode of feeding
12861	А	K103N	None	sdNVP	sdNVP	breastfed
12610	А	K103N	AZT	None	sdNVP	breastfed
13056	А	Y181C	None	None	sdNVP	formula
13270	А	Y181C	AZT	None	sdNVP	breastfed
9386	А	Y181C	None	sdNVP	sdNVP	formula
10832	А	Y181C	AZT	sdNVP	sdNVP	breastfed
12734	А	K103N	None	None	sdNVP	formula
9449	А	YI81C	AZT	cART	sdNVP	breastfed
10378	А	Y181C	None	None	None	Mixed feeding
11597	А	Y181CY/G190A	None	sdNVP	sdNVP	Mixed feeding
11667	С	M184V/Y188L	cART	cART	sdNVP	breastfed
9057	С	K103N/Y181C	None	cART	None	breastfed
10568	D	Y181C	AZT	cART	sdNVP	breastfed

Results cont...

»NNRTIs 13/46 (28%)

- Y181C in 9 and K103N 4 children respectively
- Y188L and G190A
- »NRTIs 1/46 (2%)
- M184V in one child

»Multi-class resistance 1/46 (2%)

- Child with Y188L (NNRTI) & M184V(NRTI).

Discussion

»HIV-1 subtype A more transmitted followed by C

-more women infected by HIV-1 subtype A

-high transmissibility

» Prevalence of other subtypes were A/D>D>CRF10_CD

-unique recombinant form A/D more transmitted

-D and CRFs were less transmitted

Similar pattern from review article (Karina et al. 2013).

Discussion cont..

Mutations:

- $\gg 1/3$ of sequences had major HIVDR mutations.
- -Resistance to NVP& EFZ

-sdNVP use cause cross resistance to available NNRTIs

Similar trend was seen in meta-analysis

(Arrive et al.2007)

- »None with PI major HIVDR mutation
- -PIs are not used for PMTCT
- -Very few people in the general population are on PIs.
- First line drugs in Tanzania includes (Zidovudine, Lamivudine, Tenofovir, Emtricitabine, Nevirapine, Efavirenz and Stavudine)

(National guidelines for HIV/AIDS management in Tanzania, 2012).

Discussion cont...

»M184V- in child on sdNVP;

mutation was transmitted from the mother who was on 3TC. Similar findings in Nigeria (Yang et al.2010).

»One child presented with Y181C mutation resistance to NVP and EFV -mother and infant were ART naïve)

»Multi-class resistance -Child with Y188L (NNRTI) & M184V(NRTI).

- Natural occurrence of resistance. (Nyombi et al.2008)

Discussion cont...

»PIs mutations (minor)

- -includes M36I and L33F
- -L33F is selected by Lopinavir and Atazanavir.
- -Neither mothers nor children used PIs.
- -transmitted or undisclosed ART usage
- -Available PIs in Tanzania (Lopinavir & Atazanavir).

(NACP Tanzania report 2012).

Similar scenario in Mwanza

(Kasang et al 2011)

»M36I polymorphism among 90% infected children

Similar findings Tanzania and Malawi

(Grossmann et al.2004:Nyombi et al.2008)

Limitations

»Maternal genotypes was not available to point out all cases of HIV-1 transmitted drug resistance.

»Poor record keeping on the Maternal & children drug history

»Storage time and conditions contributed to amplification failure percentage in the study.

Conclusion and Recommendations

Conclusion

- »HIV-1 subtype A was more transmitted strains or many women were infected by the virus.
- »Prevalence of major HIVDR was 28%.
- »We might miss some of the resistant strains because some may revert to wild type in the absence of ART.

Recommendations

- »Screening of HIVDR among HIV-infected children before starting ART.
- »WHO criteria for storing DBS for future use must be observed.
- »Expansion of the current study to includes maternal genotypes.

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Acknowledgement



This work was supported by collaborative funds from Fogarty HIV Research, Training Health Researchers into Vocational Excellence in East Africa (THRiVE), (grant number 087540) funded by the Wellcome Trust, KCRI, KCMU-College, GSF and Tanzania, Zambia and Botswana consortia (TanZamBo).